IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA, Plaintiff, v. ELI LILLY AND COMPANY, IMCLONE LLC, and BRISTOL-MYERS SQUIBB COMPANY, Defendants.	Civil Action No. 2:15-cv-06133-PD

DEFENDANTS' SUPPLEMENTAL CLAIM CONSTRUCTION BRIEF

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TABLE OF ABBREVIATIONS

- "**'558 patent**" refers to U.S. Patent No. 7,625,558 (Dkt. 1-1).
- "**Craven Tr.**" refers to Transcript of Rolf Craven, Ph.D., dated October 22, 2019 (Dkt. 126-1).
- "**Defendants**" refers to Defendants Eli Lilly and Company ("Lilly"), ImClone LLC ("ImClone"), and Bristol-Myers Squibb Company.
- "**Defs.' Op. Br**." refers to Defendants' Opening Claim Construction Brief (Dkt. 124).
- "**Defs.' Resp. Br.**" refers to Defendants' Responsive Claim Construction Brief (Dkt. 126).
- "**IPR**" refers to *inter partes* review.
- "**Penn**" refers to Plaintiff the Trustees of the University of Pennsylvania.
- "**Penn's Op. Br.**" refers to Penn's Opening Claim Construction Brief (Dkt. 123).
- "**Penn's Resp. Br.**" refers to Penn's Responsive Claim Construction Brief (Dkt. 125).
- "**Perez & Brady**" refers to Perez & Brady, *Principles and Practice of Radiation Oncology*, JB Lippincott Co., Phila, 2d ed. 1992 (Dkt. 104-17, Appx. 72).
- **"Tr."** refers to the Transcript of the February 5, 2020 claim construction hearing in the above-captioned litigation (Dkt. 132).

Pursuant to the Court's February 6, 2020 order (Dkt. 131), Defendants respectfully submit this supplemental brief responding to Penn's claim construction arguments presented at the February 5, 2020 *Markman* hearing.

INTRODUCTION

Consistent with the principles laid out by the Federal Circuit in *Phillips v. AWH Corp*., 415 F.3d 1304 (Fed. Cir. 2005) (*en banc*), Defendants' proposed constructions are faithful to the intrinsic record, as they are grounded in the language of the claims and the specification. Penn, on the other hand, attempts to invert the normal rules of claim construction, ignoring dispositive intrinsic evidence in favor of disfavored extrinsic evidence. The Federal Circuit has repeatedly cautioned that extrinsic evidence is less reliable than the intrinsic record and cannot be "used to contradict claim meaning that is unambiguous in light of the intrinsic evidence." *Id.* at 1324.

In both its briefing and its presentation at the *Markman* hearing, Penn committed exactly this error. Penn relies primarily—sometimes exclusively—on the testimony of its expert, Dr. Craven. Even then, Penn's reliance on expert testimony is selective. Penn has made little if any attempt to address damaging testimony provided by Dr. Craven at his deposition, taken prior to the parties' briefing. *See* Defs.' Op. Br. at 8–9, 10, 14, 15–16, 19, 21; Defs.' Responsive Br. at 3, 8–10, 13,

18, 20–21. For the reasons stated in our prior briefing as well as the hearing, the intrinsic evidence compels adoption of Defendants' constructions.

I. "kinase activity" and "kinase activity mediated by a p185 homodimer"

Claim Language	Defendants' Construction	Penn's Construction
"kinase activity" (Claims 11 and 13)	The adding of a phosphate group by an erbB receptor to a tyrosine residue of another protein	The adding of a phosphate group by a protein to another protein
"kinase activity mediated by a p185 homodimer" (Claim 13)	The adding of a phosphate group by p185 to a tyrosine residue of another protein that occurs when p185 is in a homodimer	Kinase activity mediated by p185 in its homodimeric form

- The essential dispute is whether the "kinase activity" in claim 13 is the same as the "erbB kinase activity" in claim 11.

- Based on the language and structure of the claims, the "kinase activity" in claim 13—i.e. "kinase activity mediated by a p185 homodimer"—is a specific type of "erbB kinase activity."

- Penn's argument—that the patentees would have used the phrase "said erbB kinase activity" to refer back to kinase activity in claim 11—is contrary to how the patentees refer to other claim elements.

The parties' dispute concerning these two terms can be resolved by deciding one issue: whether the "kinase activity" in claim 13 refers to the "erbB kinase activity" in claim 11. Based on the language and context of the claims and the specification's focus on targeting erbB proteins—not just any protein—"kinase activity" in claim 13 should be construed to mean erbB kinase activity, as Defendants propose.

Independent Claim 11, from which claim 13 depends, recites,

> 11. A method for inhibiting proliferation of a tumor cell, said tumor cell being from an erbB mediated tumor,
>
> which method comprises steps of:
>
> (a) contacting the cell with an antibody that disrupts ***erbB kinase activity*** said disruption having a cytostatic effect on the tumor cell; and
>
> (b) thereafter exposing the tumor cell to an effective amount of anti-cancer radiation.

'558 patent, 134:33–41 (emphasis added). Claim 11 expressly concerns "erbB kinase activity." The parties agree that a single erbB protein does not have kinase activity; rather, erbB kinase activity occurs only when two erbB proteins bind together to form a "dimer." This is important because claims 12–14, which all depend from claim 11, narrow the scope of claim 11 by specifying the type of erbB dimers having erbB kinase activity:

> 12. The method according to **claim 11** wherein the antibody inhibits kinase activity mediated by ***an EGFR homodimer***.
>
> 13. The method according to **claim 11** wherein the antibody inhibits kinase activity mediated by ***a p185 homodimer***.
>
> 14. The method according to **claim 11** wherein the antibody inhibits kinase activity mediated by ***a heterodimer of p185 and EGFR***.

Id. at 134:41–49 (emphases added). Because each dimer specified in claims 12–14 consists of erbB proteins, the kinase activity mediated by those dimers is, by

definition, erbB kinase activity. Penn's contention that "kinase activity" as used in claim 13 sweeps more broadly than erbB kinase activity ignores the structure and language of these claims.

The specification also supports Defendants' construction. The specification teaches that "***[t]he present invention*** provides a receptor-based strategy of growth inhibition which ***targets*** activated oncoprotein **receptors of the erbB tyrosine kinase family**." '558 patent, 14:51–52 (emphases added). Penn admits that the '558 patent targets erbB proteins. *See* Penn's Op. Br. at 1 ("[t]he crux of the '558 patent's inventive concept is that pretreatment of tumor cells with an ***anti-erbB*** agent having a cytostatic effect . . . ."). While Defendants' arguments are fully supported by the claims and the specification, Penn's expert also acknowledged the specification's focus on erbB kinase activity. *See* Tr. at 26:10–16 ("Q: Specifically, the specification focuses on the erbB family of kinases, right? A: The targets in the '558 patent are targeting erbB kinases.").

Penn argues that a different construction is required because claim 13 does not use the phrase "said erbB kinase activity." According to Penn, patent attorneys "don't use normal English," Tr. at 74:16, and if the patentees intended claim 13 to refer back to the erbB kinase activity recited in claim 11, "their patent counsel would have written, 'Wherein said erbB kinase activity is that mediated by a p185 homodimer.'" Tr. at 43:23–44:4. This argument puts more weight on the word "said"

than it can possibly bear. First, there is no legal requirement that a claim *must* use the word "said" to refer to a previously used term.

Second, Penn's patent attorneys did not follow such a rigid formula when referring to other claims terms. The preamble of claim 11 recites "[a] method for inhibiting proliferation of a *tumor cell*." '558 patent, 134:33 (emphasis added). The claim contains four references back to the "tumor cell," only one of which uses the cumbersome phrase "said tumor cell." *id.*, 134:34 ("said tumor cell being from an erbB mediated tumor"). In two instances, the patentees simply refer to the "tumor cell," omitting the word "said." *Id.*, 134:37–38 ("having a cytostatic effect on the tumor cell"); *id.*, 134:39 ("thereafter exposing the tumor cell . . . ."). In one instance, the patentees drop the word "tumor," just referring to the "cell." *Id.*, 134:36 ("contacting the cell with an antibody").

Penn's patent attorneys did not follow the supposed rule that Penn now seeks to impose. They did not consider it necessary to repeatedly use the phrase "said tumor cell." It is clear in the context of the claim that the "cell," "tumor cell," and "said tumor cell" all refer back to the same cell. It is just as clear that the "kinase activity" in claim 13 refers back to the "erbB kinase activity" of claim 11.

II. "disrupts erbB kinase activity"

Claim Language	Defendants' Construction	Penn's Construction
"disrupts erbB kinase activity" (Claim 11[a])	Reduces the level of tyrosine phosphorylation by erbB proteins	Disrupts the kinase activity of a member of the erbB protein family

- The parties agree that the claim requires an antibody that reduces kinase activity.

- Defendants' construction reflects the patent's consistent teaching that the antibody lowers the elevated level of tyrosine phosphorylation.

- To the extent that "disrupts" means something more than "reduces," Penn's construction renders the claim indefinite.

The parties' dispute on this term centers on whether the disruption of erbB kinase activity should be reflected by the reduction in the level of tyrosine phosphorylation by erbB proteins, as Defendants propose. Penn simply paraphrases the disputed term without providing any clarity to the factfinder. Defendants' construction should be adopted, as it accurately reflects the teaching of the specification and provides clarity to a factfinder.

Defendants' construction of this term is amply supported by the specification. For example, the patent teaches that "overexpressed p185 leads to *elevated* tyrosine kinase activity[1] which is associated with the transformed phenotype." '558 patent, 23:59–63 (emphasis added). In other words, a cancerous cell would have too much

[1] As discussed below, both parties agree that kinase activity occurs through the process of phosphorylation.

kinase activity, resulting in uncontrolled cell growth. To address this problem, the patent teaches a method that disrupts such activity by reducing the elevated level of tyrosine phosphorylation, for example, by inhibiting the formation of dimers. *Id*. at 23:62–67.

As for the meaning of "disrupts," the parties agree that "disrupts erbB kinase activity" involves, at least, a *reduction* in erbB kinase activity. *See* Tr. at 77:8–9 (statement of Penn's counsel) ("if tyrosine kinase activity is disrupted, that activity is reduced."); *id*. at 15:1–4 (Craven) ("when erbB kinase activity is disrupted, you would see a loss of kinase activity by the protein."). Penn's complaint with Defendants' construction focuses on the word "level," as Penn claims that it is difficult to measure the "level" of tyrosine phosphorylation, as it allegedly denotes to the "end result" of kinase activity. This argument should be rejected.

First, the patent itself repeatedly refers to "elevated" or "elevated level" of tyrosine kinase activity. *See, e.g.,* '558 patent, 23:57–67; 24:1–11; 12:28–33 ("[c]ells undergo erbB-mediated transformation in connection with ***elevated levels of tyrosine kinase activity*** by members of the erbB family of receptors"). Defendants' construction simply incorporates the patent's teaching on this point. It is Penn, not Defendants, who introduced the concept of a "level" of tyrosine phosphorylation into the patent.

Second, Penn's assertion that "phosphorylation" refers to an end result instead of an activity is incorrect. *See* Tr. 42:19–23. As is apparent from the parties' constructions of "kinase activity," parties agree that "kinase activity" is "the adding of a phosphate group," i.e., phosphorylation. Both parties agree that phosphorylation refers to a process. *See* Tr. at 10:6–8 ("Q. What is phosphorylation? A. Phosphorylation is that ***process*** of adding a phosphate to a substrate.") (emphasis added); *see also* Penn's Resp. Br. at 4 ("a kinase transfers a phosphate group from a donor molecule (ATP) to another protein in a ***process*** called 'phosphorylation'") (emphasis added); Craven Tr. at 85:12–22 (same).

Dr. Craven also agrees that if phosphorylation refers to the activity itself, it is readily measurable. *See* Tr. at 33:25–34:2 (Craven) ("tyrosine phosphorylation itself is measured readily in the laboratories with antibodies."); *see also id*. at 34:16–17 (Craven) ("[i]t is straightforward to analyze which proteins in the cell are phosphorylated"). Dr. Craven also agrees that for a given cell, a skilled artisan would be able to tell whether it has an elevated level of tyrosine phosphorylation. *See* Tr. at 34:21–25 ("Q. Okay. So elevated levels of tyrosine phosphorylation by erbB proteins in tumor cells, a POSA, in your opinion, is able to distinguish between an elevated and an unelevated level, correct? A. Yes."). Accordingly, a skilled artisan would be able to tell whether the activities of tyrosine phosphorylation in a tumor cell have been reduced by an antibody, as required by Defendants' construction.

Finally, to the extent that Penn argues "disrupts" means something other than "reduces," Penn's construction is indefinite as Penn claims that (1) "disrupts" means a more substantial decrease in kinase activity than "reduces," but (2) there is not a line where "reduces" ends and "disrupts" begins. *See* Tr. at 31:17–32:3 (Craven). Under Penn's construction, a defendant would not be able to tell whether it infringes the alleged invention. *See* Defs.' Op. Br. at 15–16; Defs.' Resp. Br. at 10.

III. "erbB mediated tumor"

Claim Language	Defendants' Construction	Penn's Construction
"erbB mediated tumor" (Claim 11[preamble])	Tumor whose transformed phenotype requires an elevated level of tyrosine phosphorylation by erbB proteins in tumor cells	Tumor whose transformed phenotype is associated with tyrosine kinase activity by one or more members of the erbB family of receptors

- The parties agree that an "erbB-mediated tumor" has undergone an "erbB-mediated transformation."

- Defendants' construction is based on the patent's express definition of "erbB-mediated transformation," which requires "elevated level of tyrosine kinase activity."

Defendants' construction of this term is faithful to the express definition provided by the '558 patent. In contrast, Penn relies on the extrinsic evidence to support its vague "associated" construction, ignoring dispositive intrinsic evidence.

Dr. Craven's testimony on this term tracks Penn's argument with regard to the term "disrupts erbB kinase activity." Dr. Craven claimed that it is difficult to measure elevated level of tyrosine phosphorylation. Tr. at 79:2–6. However,

Defendants' construction comes from Penn's own definition included in the '558 patent, which explicitly ties "erbB-mediated" to "elevated level of tyrosine kinase activity." *See* '558 patent, 12:28–33 ("[c]ells undergo erbB-mediated transformation in connection with ***elevated levels of tyrosine kinase activity*** by members of the erbB family of receptors"); *see also* Defs.' Op. Br. at 11–14; Defs.' Resp. Br. at 11–13. Such an express definition is binding. *See Braintree Labs., Inc. v. Novel Labs., Inc*., 749 F.3d 1349, 1356 (Fed. Cir. 2014) ("Under our precedent, the patentee's lexicography *must* govern the claim construction analysis") (emphasis added).

Moreover, Defendants' construction makes clear that the elevated level of tyrosine kinase activity *causes* the transformed phenotype, a point supported by the clear teaching of the specification. *See* Defs.' Op. Br. at 13–14; Defs.' Resp. Br. at 12. Dr. Craven conceded as much at the hearing. *See* Tr. at 79:12–80:2 (discussing that to identify an erbB-mediated tumor, a skilled artisan would check whether the disruption of erbB kinase activity leads to the death of tumor cells or a reversion to "a more normal phenotype").

IV. "contacting the cell with an antibody" and "said tumor cell being from an erbB-mediated tumor"

Claim Language	Defendants' Construction	Penn's Construction
"contacting the cell with an antibody" (Claim 11[b])	Placing the antibody into direct physical contact with the cell rather than administering the antibody intravenously	Administering an antibody that interacts with the cell
"said tumor cell being from an erbB-mediated tumor" (Claim 11[preamble])	A transformed tumor cell removed or derived from an erbB mediated tumor	The tumor cell is from a tumor whose transformed phenotype is associated with tyrosine kinase activity by one or more members of the erbB family of receptors

- The essential dispute is whether claim 11 encompasses *in vivo* methods.

- Under the doctrine of claim differentiation, the scope of claim 11 is presumptively different from that of claim 1, which clearly claims an *in vivo* method.

- Penn's constructions ignore the differences in language between claims 1 and 11.

- Penn's interpretation of the claims treats claim terms, such as "therapeutically," as mere surplusage.

The fundamental issue for the Court is whether claim 11 recites an *in vitro* method (as Defendants contend) or whether the claim encompasses both *in vitro* and *in vivo* methods (as Penn alleges).[2]

[2] *In vivo* methods refer to studies conducted on living organisms, such as humans or other animals. *In vitro* (literally, "in glass") methods refer to experiments not (continued…)

The ’558 patent contains two different types of claims. Independent claims 1, 5, 6, 26, and 27 claim “method[s] of treating an individual.” By contrast, independent claims 7 and 11 do not mention an “individual”; instead, they recite “method[s] for inhibiting the proliferation of a tumor cell.” Under the doctrine of claim differentiation, the differences in claim language[3] create a presumption that the scope of the claims are different. *Comark Commc’ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187–88 (Fed. Cir. 1998).

Defendants’ proposed constructions properly acknowledge the differences between the two sets of claims. With respect to “contacting the cell with an antibody,” Defendants’ construction makes clear that Claim 11 is limited to delivering the antibody in ways that are appropriate for *in vitro* experiments. Defendants’ construction of “said tumor cell being from an erbB-mediated tumor” makes clear that the claim is directed to a method of inhibiting the proliferation of “a cell,” not the treatment of an individual. A scientist might want to work with cells rather than a tumor because a tumor contained in a human (or animal) body (i.e., *in vivo*) contains non-cancerous cells as well as blood vessels. *See* Defs.’ Resp. Br. at

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conducted on an entire organism, such as experiments conducted in a test tube or petri dish.

[3] This is just one example of the difference in language between the two sets of claims. Additional differences are discussed in Defendants’ Opening Claim Construction Brief. Defs.’ Op. Br. at 17–18.

18–19. When the patentees intended to claim methods of treating *tumors*, as opposed to testing an antibody in tumor cells, they made that clear. *See* Defs.' Op. Br. at 17–19.

Penn ignores the differences in language between the two sets of claims and attempts to construe claim 11 to be commensurate with claim 1. On cross-examination, Penn's expert admitted that, under his reading of the claims, claims 1 and 11 both cover the same subject matter—*in vivo* and *in vitro* methods. Tr. at 85:17–19 ("Q. So in your view, Claim 1 and Claim 11 are both drawn to both in vivo and in vitro methods, correct? A. That is correct.").

This misreading of the claim is reflected in Penn's claim constructions. For example, claims 1 and 11 use different verbs to describe how the antibodies reach their target. Claim 1 requires "administering" an antibody to an individual, while claim 11 requires "contacting the cell with an antibody." *Compare* '558 patent, 133:21 *with* '558 patent, 134:36. Penn's expert has admitted that "administering" is different than "contacting." Craven Tr., 111:10–14 ("Q. So there's a difference between the phrase 'contacting the cell with an antibody' and 'administering an antibody.' Is that what you're saying? A. Yes. I think there is a distinction.") Yet, in its construction, Penn replaces "contacting" with "administering," obliterating the very distinction its expert acknowledged.

Penn's interpretation of claim 11 violates another principle of claim construction; Penn effectively reads out claim terms as surplusage. Courts should avoid adopting constructions that would "render additional, or different, language in another independent claim superfluous." *AllVoice Computing PLC v. Nuance Commc'ns, Inc.*, 504 F.3d 1236, 1247 (Fed. Cir. 2007); *see also Texas Instruments Inc. v. U.S. Int'l Trade Com'n*, 988 F.2d 1165, 1171 (Fed. Cir. 1993) (rejecting the construction that would render claim limitation "mere surplusage"). This is exactly what Penn advocates here. For example, claim 11 recites the use of "an effective amount of anti-cancer radiation," while claim 1 adds the word "therapeutically" and refers to the use of "a ***therapeutically*** effective amount of anti-cancer radiation." '558 patent, 133:26–27. Under Penn's construction, the addition of the word "therapeutically" in claim 1 is mere surplusage, as Dr. Craven admitted. *See* Tr. at 86:15–19 ("Q. So in your view, the word 'therapeutically' in Claim 1 in step (b) is redundant or surplusage? . . . A. Yes, I think that's correct."). Accordingly, such a construction that introduces surplusage should be rejected.

V. "cytostatic effect"

Claim Language	Defendants' Construction	Penn's Construction
"cytostatic effect"	Plain and ordinary meaning	Inhibition or suppression of cell growth and multiplication

- In light of Penn's admission that its proposed construction permits an antibody to have both cytostatic and cytotoxic effects, Defendants agree to adopt Penn's construction.

Defendants agree to Penn's proposed construction of "cytostatic effect" as "inhibition or suppression of cell growth and multiplication."

The key dispute had been whether an antibody can have more than one effect—in particular, whether an antibody can have both a "cytostatic effect" and a "cytotoxic effect." In the *inter partes* review, the Patent Office held that an antibody can have both a cytostatic and cytotoxic effects. *See* Dkt. 61-1 at 31–32. The Federal Circuit affirmed the decision of the Patent Office. Dkt. 67-1. Penn nevertheless argued in its claim construction briefs that both the Patent Office and Federal Circuit were wrong, because "[an] antibody cannot have both a cytostatic and cytotoxic effect on **a** single tumor cell." Penn's Resp. Br. at 17.

Penn's argument was inconsistent with its prior statements to the Patent Office. During the *inter partes* review, Penn stated:

> I also wanted to go back and emphasize that *antibodies can have many different effects.* They can be blocking, they can be agonistic, they can be cytostatic and they can

> be cytotoxic. *Cytostatic is not the opposite of cytotoxic.* So I just wanted to make sure that that was understood, too.

Eli Lilly and Company v. Trustees of the University of Pennsylvania, IPR2016-00458, Paper 89 (PTAB Mar. 29, 2017) at 61:22–62:2 (emphases added). Penn also agreed that cytostatic and cytotoxic effects are "not mutually exclusive either." *Id.* at 62:3–10.

At the *Markman* hearing, Penn conceded that an antibody can, indeed, have both a cytostatic and cytotoxic effect. Penn's expert, Dr. Craven, admitted that "most agents are not amenable to a bright line analysis of being only a cytostatic agent or only a cytotoxic agent." Tr. at 93:13–16. As Penn's counsel later confirmed,

> *We're not saying definitively that there can never be both a cytostatic effect and a cytotoxic effect from the antibody.* Dr. Craven just talked about how that can happen. But there's no reason to construe the term "cytostatic effect" as something beyond inhibition or suppression of cell growth and multiplication. We can argue later, when we're dealing with particular prior art references, particular therapies treating particular tumor cells. We can argue then about does this have a cytostatic effect, does it *also* have a cytotoxic effect.

Tr. at 101:21–102:5 (emphases added). Penn's admission resolves the only dispute between the parties.

With the understanding that Penn's construction allows for an antibody to have multiple effects, including both cytostatic and cytotoxic effects, Defendants agree to adopt Penn's construction.

VI. "anti-cancer radiation"

Claim Language	Defendants' Construction	Penn's Construction
"anti-cancer radiation"	Radiation that kills cancer cells, regardless of the type or source of the radiation	Conventional, established radiation therapies used at the time of the filing to treat cancer patients

- Defendants' construction reflects the plain and ordinary meaning of the term "anti-cancer radiation."

- Statement that certain types of radiation *can be* used as part of the claimed method is not a disavowal of other types of radiation.

A Court may only depart from the plain and ordinary meaning of a claim term in two circumstances: (1) when the patentee "acts as his own lexicographer," providing express definitions, or (2) "when the patentee disavows the full scope of a claim term either in the specification or during prosecution." *Thorner v. Sony Comput. Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). The '558 patent does not define "anti-cancer radiation." At the hearing, Penn argued that the '558 patent disavows radioimmunotherapy ("RIT"), or any experimental radiation therapy as of 1998, because the specification "said over and over again the present invention *can* be used with conventional, established anti-cancer radiation therapies with protocols and parameters." Tr. at 116:18–22 (emphasis added). But there is nothing in the specification that disavows RIT or any other type of radiation.

"The standard for disavowal of claim scope is . . . exacting." *Thorner*, 669 F.3d at 1366. Evidence of disavowal must be both clear and unambiguous, such as

"expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Id*. Statements such as "the present invention requires" or "all embodiments of the present invention are ...." may amount to disavowal. *Hill-Rom Servs., Inc. v .Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (internal citation omitted). By contrast, permissive language—that certain features "can be used" or are included in "preferred embodiments"—does not rise to the level of disavowal. *See, e.g.*, *Abbott Labs. v. Baxter Pharm. Prod., Inc*., 334 F.3d 1274, 1280 (Fed. Cir. 2003) (finding that statements in the specification that certain amounts "can be used" is "far from an express disavowal of other effective amounts").

Penn relies on the following passages from the '558 patent as evidence of disavowal:

- "Inhibition mediated by the introduction of mutant p 185neu receptors causes synergistic growth inhibition when combined with conventional cytotoxic agents such as gamma-irradiation. The present invention provides methods of treating many epithelial solid tumors since the methods of the invention complement the use of already established treatment modalities." '558 patent, 18:48–54.
- "Thus, once the active agent inhibits the kinase activity, exposure to radiation may follow suit. Gamma radiation is delivered according to standard radiotherapeutic protocols using standard dosages and regimens." *Id*. at 26:24–28.
- "By combining biologic inhibition of signaling with agents capable of specifically inhibiting receptor oncoproteins of the tyrosine kinase family, we may be able to influence the kinetics of tumor cell response to standard cytotoxic agents." *Id*. at 55:22–26.

But none of these passages contain any "expression[] of manifest exclusion or restriction." *Thorner*, 669 F.3d at 1366. At most, these passages identify "cytotoxic agents" that *can be* used. The patent never says that any particular type of radiation *must* be used.

The specification passages Penn cites lend no support that the alleged invention is limited to "conventional, established radiation therapies used at the time of the filing to treat cancer patients." All of those passages fall within the "Description of the Preferred Embodiment" section of the '558 patent. "Because these references refer only to preferred embodiments and not the invention as a whole, the specification passages do not support the limitation imported into the claims." *Abbott Labs.*, 334 F.3d at 1279. And in the "Summary of the Invention" section of the '558 patent, the patent refers to "anti-cancer radiation" or "radiation" in a generalized manner, and never for once restricts it to "conventional" or "established" therapies. *See* '558 patent, 4:6–10:23.

Nor does Penn point to any disclosure in the specification that would cause a skilled artisan to believe that it is essential for the alleged invention to use conventional radiation therapies that existed in 1998 (as opposed to potentially more-effective radiation therapies that could be developed in the subsequent twenty years). Without any such evidence, the additional limitation should not be read into the claims. *See Blackbird Tech LLC v. ELB Elecs., Inc.*, 895 F.3d 1374, 1378 (Fed.

Cir. 2018) (refusing to read in additional limitation because the specification or prosecution history provides no suggestion that such limitation is "important, essential, or critical to the invention").

In contrast, Defendants' construction is faithful to the plain meaning of the term and is supported by the specification. "Anti-cancer radiation" has a plain meaning that is readily understandable by a lay person—radiation that kills cancer cells. The specification discloses many types of radiation therapies that could be used for the alleged invention, including X-ray, gamma radiation, and any treatment options disclosed by Perez & Brady. *See* '558 patent, 18:13–19 (Perez & Brady, "which is incorporated herein by reference describes radiation therapy protocols and parameters which can be used in the present invention.").

RIT is one of the radiation therapies expressly disclosed in Perez & Brady. *See* Perez & Brady at 162. Indeed, Perez & Brady has a whole chapter directed to RIT. *Id*. It is well-known to a skilled artisan that RIT kills cancer cells and in 1998 was used in clinical trial to treat cancer patients. Since neither the specification nor the prosecution history disavows RIT, RIT is within the scope of the claim term.

CONCLUSION

For the reasons explained above, Defendants respectfully request that the Court adopt their proposed constructions of the disputed terms.

Dated: February 21, 2020

Respectfully submitted.

/s/ Matthew Kudzin

Nicole D. Galli (PA Id. #78420)
ndgalli@ndgallilaw.com
Law Offices of N.D. Galli LLC
2 Penn Center Plaza, Suite 910
1500 JFK Blvd. Philadelphia, PA 19102
Telephone: 215-525-9580
Facsimile: 215-525-9585

George F. Pappas (*pro hac vice*)
gpappas@cov.com
Michael N. Kennedy (*pro hac vice*)
mkennedy@cov.com
Matthew Kudzin (*pro hac vice*)
mkudzin@cov.com
COVINGTON & BURLING LLP
850 Tenth Street, NW
Washington, DC 20001-4956
Telephone: 202-662-6000
Facsimile: 202-662-6291

Jennifer L. Robbins (*pro hac vice*)
jrobbins@cov.com
COVINGTON & BURLING LLP
620 Eighth Avenue
New York, NY 10018-1405
Telephone: 212-841-1180
Facsimile: 212-841-1010

Patrick N. Flynn (*pro hac vice*)
pflynn@cov.com

COVINGTON & BURLING LLP
3000 El Camino Real
5 Palo Alto Square, 10th Floor
Palo Alto, CA 94306-2112
Telephone: 650-632-4732
Facsimile: 650-632-4800

Attorneys for Defendants Eli Lilly and Company, ImClone LLC, and Bristol-Myers Squibb Company

CERTIFICATE OF SERVICE

I hereby certify that on February 21, 2020, I caused the foregoing document to be filed electronically through the Court's Electronic Case Filing ("ECF") system. Pursuant to Local Rule 5.1.2, this document is being served on all counsel of record by operation of the Court's ECF system.

/s/ Matthew Kudzin
Matthew Kudzin